

Roche perspectives on Tamiflu

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Oseltamivir was the first orally active, direct-acting antiviral developed for influenza and was generated through a process of rational drug design [1]. Oseltamivir is indicated for the treatment and prophylaxis of influenza [2,3], and extensive clinical data support its efficacy and safety [4–12]. It is the standard of care for treatment of seasonal influenza [13,14], forms the backbone of many national pandemic preparedness plans [15,16] and has also been included on the World Health Organization essential medicines list since 2009 [17].

To support the registration of oseltamivir, an extensive clinical trial programme was conducted by Roche, primarily between 1997 and 2002. It was first approved in Switzerland in 1999 and is currently approved in over 100 countries worldwide. Since the initial approval, Roche has continued to conduct supplementary studies to expand the body of evidence supporting oseltamivir's clinical efficacy and safety. These studies have, for example, supported the introduction of a paediatric suspension, and a recent marketing authorization application to extend the treatment indication to infants younger than 1 year (approved in the United States). Studies to monitor cases of resistance are also ongoing.

All of these studies were conducted to the highest regulatory standards of the time, and the studies that supported the initial registration were subject to audit by Roche's quality assurance department and the US Food and Drug Administration. The data and reports provided by Roche to health authorities have always been in full accordance with the specific requirements of each country where we have sought a license. Clinical data from Roche-sponsored and -supported studies have been published in peer-reviewed journals, starting with the two pivotal adult oseltamivir treatment studies, which were published in 2000 [4,5]. Over the next 14 years, additional data were published for a variety of indications in different patient groups, including a pivotal paediatric trial [6], postexposure prophylaxis [7,8], children with asthma [9], seasonal

prophylaxis in immunocompromised patients [10], resistance surveillance [11], and treatment for infants [12], elderly and chronically ill patients [18,19].

As evidenced by our actions, Roche firmly believes in the dissemination of data to the scientific and medical communities. In recent years attitudes towards sharing clinical trial data have gradually changed among patients, governments and regulators. Roche has responded to these changes; summary data and protocols for all 77 Roche-sponsored oseltamivir studies can now be accessed online (www.roche-trials.com). Any investigator wishing to analyse individual patient data (IPD) or to receive clinical study reports (CSRs) can apply for access (www.clinicalstudydatarequest.com). As part of the process to access IPD, the investigator is asked to submit a research proposal for review by an independent panel, which will consider a number of factors such as the scientific value of the question posed, whether available data can support the proposed analysis and the investigators' qualifications and experience to conduct the research.

The changes that have led the scientific community to this point have developed over many years, and this debate is by no means complete. Indeed, among both patients and physicians there is still a substantial degree of caution around the mechanisms and privacy measures in place for sharing medical data [20]. However, Roche believes that enough progress had been made, and that the advances in technology are sufficient, to allow greater sharing of data in a manner conducive to high-quality research while protecting the integrity of the valuable relationship we have with patients who participate in our clinical trials.

The request that Roche received from the Cochrane Acute Respiratory Infections (ARI) Group in 2009 should be viewed against this context, since it was unprecedented in a number of ways:

- A large amount of clinical data was requested, including IPD, which were not typically provided to non-statutory bodies at that time.
- The primary stakeholder with whom Roche data is shared was, and continues to be, regulatory authorities. This was the only type of data sharing envisaged by the consent

forms that patients had signed prior to enrolment in any clinical study.

- Requiring such detailed data was also a departure for the Cochrane Collaboration, who typically analysed summary data only.

Nonetheless, recent experience with the Cochrane Collaboration and oseltamivir has helped to shape the current Roche Global Policy on Sharing of Clinical Trials Data [21], which was implemented in June 2013 and is at the forefront of the data sharing movement. Roche believes that data from clinical trials should be made available to both physicians and patients to help them make the most informed decision possible when choosing between treatment options. This should apply to both clinical studies sponsored by pharmaceutical companies as well as those conducted by academic institutions and governments. In fact, sharing clinical trial data could enhance the trust that patients who enrol in studies have in companies such as Roche.

Sharing clinical study reports with the Cochrane Acute Respiratory Infections Group

With the establishment of the data sharing policy, Roche started to work towards meeting the Cochrane ARI Group's request for access to full CSRs, including IPD. Each individual CSR had to be redacted to remove patient identifiers, such as demographic or geographical information, as well as the names and contact details of investigators, vendors and Roche staff. As this was a lengthy process, CSRs were delivered in batches between June and November 2013.

Results from the Cochrane ARI Group's analysis of oseltamivir clinical trial data were published in April 2014 [22], and despite their request for IPD, they did not make use of it. Roche disputes the findings and conclusions of this revised report. Some of the issues have been briefly touched upon in the Roche response published in the *British Medical Journal* [23], and a detailed 70-page critique of their review has been published on the Cochrane Editorial Unit website (<http://editorial-unit.cochrane.org/cochrane-review-neuraminidase-inhibitors-influenza>) [24]. To briefly summarize some key topics covered in this critique, problems with the Cochrane ARI Group's review include: application of flawed methodology to the assessment of the symptom alleviation data; misrepresentation of the clinical value of prophylaxis; consideration of safety data from only a subset of the studies that were provided; and inappropriate analysis of these safety data [24]. Roche welcomes the constructive interaction we have been able to have

with the Cochrane editorial unit and are pleased that they have agreed to host our critique on their website.

In addition to the specific shortcomings of the Cochrane ARI Group's review, the Cochrane Collaboration's approach of restricting analyses to randomized controlled trials (RCTs) means that valuable data from other sources were not considered. Extensive safety data, collected during 15 years of oseltamivir use, were not taken into account in this review; nor were the abundance of observational data, including those generated during the 2009–2010 influenza pandemic, which repeatedly show the clinical benefits of oseltamivir and build on the findings of the RCTs. One example is the impact of oseltamivir on secondary complications of influenza infection. Analyses of data from RCTs conducted by several different groups have consistently found evidence of an effect: the primary analysis by Jefferson et al. [22] showed a reduction in the incidence of pneumonia, and the meta-analyses by Kaiser et al. [25], Hernán and Lipsitch [26] and Ebell et al. [27] all found a reduction in lower respiratory tract complications requiring antibiotics. These analyses were in settings where complication rates are not particularly high, but they predict that at a population level or in the case of more severe disease, e.g. during a pandemic, similar reductions would be observed. Indeed, as far back as 1969, Wingfield et al. [28] reported the effect of an adamantane drug on influenza and hypothesized about the benefit antivirals could bring to reducing secondary complication rates. Understanding of the biologic relationship between viral infection and secondary bacterial infections has grown since then, but it still points towards that same hypothesis [29–31], and indeed observational data supports this [32–34]. The combined data sets of the RCTs and the observational studies form a coherent whole, and it is entirely appropriate to consider them together. It is likely that any future influenza antiviral therapy would rely on a similar combination of RCT and observational or real-world data to understand the full spectrum of its benefits.

Roche considers that the inconsistent and inaccurate analysis methods used by the Cochrane ARI Group, as detailed previously [24], as well as the analysis's exclusion of two major sources of data, have resulted in inappropriate conclusions being drawn regarding the efficacy and safety of an established influenza medicine. These conclusions risk causing confusion among patients and physicians and could lead to public health concerns if patients do not comply with their prescribed medicine. In this context, it is important to note that use of oseltamivir for the treatment of influenza continues to be endorsed by the US and European Centers for Disease Control and Prevention (CDC and ECDC), Public Health England, the Infectious Diseases Society of America and others [35–38].

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